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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/537,950	HWA ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 10 October 2008 are acknowledged and the amendments are entered.

Claims 1-24 are pending and examined in this Office action.

Withdrawn Objections/Rejections

The objection to claim 23 because of informalities is withdrawn in view of amendments filed to the instant claim on 10 October 2008.

The rejections of claims 1-20 and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments filed to the instant claims on 10 October 2008.

ALL of the prior art rejections are withdrawn in view of amendments filed to the instant set of claims on 10 October 2008. ALL of the prior art rejections are newly applied and are necessitated by amendment.

Claim Rejections - 35 USC § 101

The following rejection is NEWLY applied under a new grounds:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

These method claims of the instant application (instant claims 1-24) recite a series of steps without a physical transformation. Further, the claims fail to recite a tie to a machine. It is noted that while the result of the calculation is output to a user, this final step is an insignificant post-solution activity and does not constitute a significant tie to another category of invention. It is noted that while instant claim 1 has the physical step of implementing interactions among a plurality of proteins, this physical step does not constitute a physical transformation because no matter is transformed.

Response to arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive. Applicant argues that the amended version of the instant set of claims recite a physical transformation with regard to gene expression. This argument is not found to be persuasive because the amended claim recites "for generating an output CORRESPONDING TO a desired gene expression upon binding of two or more regulatory proteins..." which is an intended "use" and is not an active method step. Consequently, the output generated by the process must only CORRESPOND TO the desired gene expression. In other words, no gene expression (i.e. physical transformation) is required as part of the scope of the instantly rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35 U.S.C. 103 Rejection #1:

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. [US Patent 5,814,618; issued 29 September 1998; filed 7 June 1995; on IDS and corresponding WIPO search report] in view of Wasiewicz et al. [Cybernetics and Systems: An International Journal, volume 31, 2000, pages 283-315 (obtained in a version where pages are numbered consecutively starting at 1)].

Claim 21 is drawn to a method of genetic computing by encoding control functions in regulatory DNA sequences for controlling gene expression, the method comprising:

--selecting a relative binding strength and a relative binding position of individual binding sites within a cis-regulatory region of one or more regulatory DNA sequences to exert combinatorial control of gene expression to operate as at least one logic function selected from a plurality of different logic functions for generating an output corresponding to a desired gene expression upon binding of two or more regulatory proteins, wherein each different logic function corresponds to a different gene expression.

The patent of Bujard et al. examines the methods for regulating gene expression. Specifically, Bujard et al. regulates gene expression using tetracycline-responsive fusion proteins. The abstract of Bujard et al. teaches the use of two distinct ("heterologous") polypeptides as part of a fusion protein in which the first polypeptide binds to a tet operator sequence **AND** the second polypeptide inhibits transcription in eukaryotic cells (consequently a logical function using the "AND" operator exists). The peptides bind with the nucleotide sequence at relative binding positions. Additionally, the relative binding strength between the peptides and the nucleotides is regulated to a desired expression level through modulating the concentration of tetracycline [i.e. see Figure 8 of Bujard et al. for output corresponding to a desired level of expression that is tuned using tetracycline]. Figures 6 and 9 of Bujard et al. illustrate the cis-regulatory site arrangement within the gene.

Bujard et al. does not teach genetic computing, per se, wherein each different logic function corresponds to a different gene expression.

The article of Wasiewicz et al. studies inference based on molecular computing. Specifically, Figure 1 on page 3 of Wasiewicz et al. illustrates an analytical representation of DNA oligonucletides wherein each logic function corresponds to a different set of genes that express differently.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the controlling function in regulatory DNA sequences in Bujard et al. by use of the genetic computing methods wherein each different logic function corresponds to a different gene expression in Wasiewicz et al. wherein the motivation would have been that the genetic computing methods with distinctly expressed logic functions of Wasiewicz et al. has the advantage of identifying problems that can be solved by molecular computing more efficiently that on classical electronic machines. There would have been a reasonable expectation of success in combining the empirical study of Bujard et al. with the computational study of Wasiewicz et al because both studies are drawn to analogous principles controlling transcription of DNA using logic functions to solve biological problems.

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant first argues on page 8 of the Remarks that Bujard et al. teach binding of a single fusion protein, that has TWO DISTINCT polypeptides, which is different from binding of two or more regulatory proteins as claimed. Applicant continues to argue that domains of proteins may have diverse functions, but are still part of the same protein unit. This argument is not found to be persuasive because a fusion protein is, by definition, the fusion of two proteins together through transcription and translation of genes. Absent a definition from the specification, a fusion protein is interpreted to comprise two proteins (or two DISTINCT polypeptides, as argued by applicant) that are attached or "fused" together.

Applicant argues that the fusion protein involved in both the DNA binding and interaction is represented by only a single input in Bujard et al. This argument is not persuasive because limitations governing the number of inputs are not recited in the instantly rejected claim.

Applicant argues that Bujard et al. do not disclose binding of two or more regulatory proteins and is unable to exert combinatorial control of gene expression necessary to construct logic functions. This argument is not found to be persuasive as the differing gene expression pertaining to different logic functions is taught in Wasiewicz et al.

35 U.S.C. 103 Rejection #2:

Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21

above, in further view of Kirch et al. [Oncogene, 1999, volume 18, pages 2728-2738, on previous 892 form] in view of Orkin [Cell, volume 63, 1990, pages 665-672].

Claim 1 is drawn to a method for controlling the transcription of target genes by genetic computing, the method comprising:

--identifying a plurality of logic function, each logic function having an output corresponding to a different gene output signal;

--selecting at least one logic function corresponding to a desired target gene output signal; and

--implementing the at least one logic function by producing interactions among a plurality of regulatory proteins and interactive binding of two or more regulatory proteins at corresponding binding sites of the target genes, wherein the target genes each comprise one or more cis-regulatory regions having individual DNA binding sites, and wherein each binding site has a binding strength and binding location which are adjustable by varying composition of the one or more cis-regulatory regions;

--wherein the interactions comprise contact interactions and long-distance interactions that avoid interference between the DNA binding sites.

Claim 11 is drawn to a method for genetic computing using combinatorial transcription control comprising:

--identifying a plurality of logic functions, each logic function having an output corresponding to a different gene expression;

--selecting at least one logic function corresponding to a desired gene expression; and

--implementing the at least one logic function by producing interactions among a plurality of transcription factors and interacting binding of two or more transcription factors at corresponding binding sites of one or more target genes, wherein the target genes each comprise one or more cis-regulatory regions having individual DNA binding sites, and wherein each binding site has a binding strength and a binding location which are adjustable by varying composition of the one or more cir-regulatory regions.

The patent of Bujard et al. and study of Wasiewicz et al. make obvious the methods for regulating gene expression based on genetic computing, as discussed above. Specifically, Bujard et al. regulates gene expression using tetracycline-responsive fusion proteins. Lines 54-60 of column 2 of Bujard et al. elaborate:

> In a preferred embodiment, the method involves introducing into the cell a nucleic acid molecule encoding a fusion protein which inhibits transcription, the fusion protein which inhibits transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells; and modulating the concentration of a tetracycline, or analogoue thereof, in the subject. As used herein, the term "heterologous" used in reference to the second polypeptide is intended to indicate that the second polypeptide is derived from a different protein than the first polypeptide.

Consequently, the logical function is identified as two fused polypeptides collectively regulating the tet operator sequence **AND** expression in eukaryotic cells. Furthermore, the invention of Bujard et al. implements this logic function using the two distinct, regulatory proteins. The target tet repressor/operator/inducer system of sequences is on a gene molecule as illustrated in Figures 6 and 9 of Bujard et al.; this type of arrangement is "cis-regulatory." Additionally, the cited passage above indicates that the binding of the peptides to the regulatory factors are adjusted through changing the composition of this cis-regulatory region by the addition of tetracycline, which alters the binding strength and location of the peptides (i.e. at a high tetracycline

concentration, binding at a particular location is inhibited). The article of Wasiewicz et al. studies inference based on molecular computing. Specifically, Figure 1 on page 3 of Wasiewicz et al. illustrates an analytical representation of DNA oligonucletides wherein each logic function corresponds to a different set of genes that express differently.

However, Bujard et al. and Wasiewicz et al. do not teach adjusting the actual composition of the nucleic acid sequence in the cis-regulatory region itself in order to adjust transcription. Additionally, Bujard et al. does not teach the role of protein-protein interactions in regulating transcription, nor does Bujard et al. teach long distance and contact interactions.

The article of Kirch et al. studies that the expression of human p53 requires synergistic activation of transcription from the p53 promoter by AP-1, NF-kB, and Myc/Max. Specifically, Kirch et al. illustrates in Figure 2 on page 2730 that mutating the sequence composition at either the AP-1, NF-kB, or Myc/Max locus significantly reduces or eliminates transcription.

Bujard et al., Wasiewicz et al., and Kirch et al. do not teach the role of protein-protein interactions in regulating transcription, nor does Bujard et al. teach long distance and contact interactions.

The review of Orkin studies the regulations of genes in globins.

Specifically, the summary of the Orkin states on page 671:

> We can be optimistic that further dissection of LCRs will delineate DNA sequences critical for these effects and associated proteins. The interaction of LCRs with individual genes must depend on specific protein-protein interactions , most likely involving a small, but elite, group of regulators.

Consequently, specific protein-protein interactions affect the transcription of erythroid related genes at "locus controlled regions." These contact interactions between proteins, in turn, result in long distance interactions in transcription regulation with genes more than 20 kb upstream of the LCR site [see last paragraph on page 665 of Orkin].

Claims 3 and 13 are further limiting wherein the logic function selected comprises "AND." As highlighted above, the logical function comprises the operator "AND."

Claims 5 and 15 are further limiting wherein at least one of the interactions among the regulatory proteins comprise specific protein-protein interactions. Orkin teaches specific protein-protein interactions in the summary on page 671 of the article.

Claims 7 and 17 are further limiting wherein the interactive binding comprises tunable specific protein-DNA interactions which are tunable by selecting the binding strengths. As explained in lines 54-60 of column 2 in Bujard et al., tetracycline concentration is used to modulate the binding of the peptides in the fusion protein to the tet operator sequences. Additionally, Kirch et al. tunes transcription through mutation of the nucleic acid sequence at given locus.

Claims 8 and 18 are further limiting wherein the one or more cis-regulatory regions include long distance repression and activation schemes. These long distance

interactions in transcription regulation with genes more than 20 kb upstream of the LCR site are taught in the last paragraph on page 665 of Orkin.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the method of gene regulation and computation of Bujard et al. and Wasiewicz et al. by the regulation of human p53 production in Kirch et al. wherein the motivation would have been that the control of p53 transcription via mutation plays a significant role in mitogenic stimulation and differentiation, and results in a regulation of p53 in tumors [see last paragraph of introduction]. It would have been further obvious to modify the regulation of genetic expression in Bujard et al., Wasiewicz et al., and Kirch et al. by use of the long-distance transcriptional regulation and, protein-protein interactions in Orkin wherein the motivation would have been that long-distance regulation of gene expression based on specific protein-protein interactions has a significant role in understanding developmentally regulated, multigene loci not specific to globins [see summary of Orkin on page 671].

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant first argues that even though a logic operation is performed in Bujard et al., it is performed by mere chance and that nothing in Bujard et al. teaches or suggests that a plurality of different logic functions can be executed by combinatorially controlling

transcription. These arguments are not found to be persuasive because as applicant argues, Bujard et al. does teach a logic function; whether it is intended or coincidence does not disqualify it from being such a logic function. Additionally, the reference of Wasiewicz et al. teaches the plurality of different logic functions executed by combinatorially controlling transcription.

35 U.S.C. 103 Rejection #3:

Claims 2 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Kirchhamer et al. [PNAS, volume 93, 1996, pages 9322-9328].

Claims 2 and 12 are further limiting wherein the regions are modular.

Bujard et al., Wasiewicz et al., Kirch et al., and Orkin make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al., Wasiewicz et al., Kirch et al., and Orkin do not show that each of their processes is modular.

Kirchhamer et al. studies modular cis-regulatory organization of developmentally expressed genes with specific examples including two genes transcribed in the sea urchin embryo.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcriptional regulation methods of Bujard et al., Wasiewicz et al., Kirch et al., and Orkin by use of the modular cis-regulatory regions of

Kirchhamer et al. wherein the motivation would have been that by understanding the subelements of the cis-regulatory systems as control modules, a more overall pattern of developmental gene expression can be assembled and understood [see last sentence of the introduction on page 9322 of Kirchhamer et al.]

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Kirchhamer et al. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

35 U.S.C. 103 Rejection #4:

Claims 4, 6, 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Renkawitz [Trends in Genetics, 1990, volume 6, pages 192-197].

Claims 4 and 14 are further limiting wherein at least one of the interactions among the regulatory proteins comprise non-specific protein-protein interactions controlled by selecting binding locations.

Claims 6 and 16 are further limiting wherein at least some of the interactions among the regulatory proteins comprise protein-protein interactions mediated by collaborative competition between the regulatory proteins and a glue-like DNA-bound protein or protein complex.

Bujard et al., Wasiewicz et al., Kirch et al., and Orkin make obvious a method of regulation transcription using interactions and logical operations, as discussed above. Additionally, Bujard et al., Wasiewicz et al., Kirch et al. and Orkin discuss specific protein-protein and protein-DNA interactions. Orkin teaches distal, long-distance interactions in the paragraph bridging pages 665-666 of the review. However, Bujard et al., Wasiewicz et al., Kirch et al., and Orkin do not show non-specific interactions or competitive binding.

The article of Renkawitz reviews transcriptional repression in eukaryotes.

Specifically, Figure 1A on page 193 of Renkawitz illustrates competitive binding of trans-activating domains to DNA binding sites with generic, non-specific inhibitor proteins. The objective of this competitive binding is to further regulate transcription.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., and Orkin by use of competitive inhibition with non-specific protein-DNA interactions of Renkawitz wherein the motivation would have been that competitive binding gives additional variables and controls for regulating transcription of a desired gene (i.e. see Figure 1 on page 193 of Renkawitz, the text in the caption and underneath the diagram).

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Renkawitz. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

35 U.S.C. 103 Rejection #5:

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Ogawa [US Patent 5,535,382; issued 9 July 1996; filed 17 November 1993].

Claims 9 and 19 are further limiting comprising after the step of identifying the at least one logical function:

--reducing the at least one logic function to a minimal conjunctive normal form; and

--implementing a first clause as an activation clause and all remaining clauses as repression clauses;

--wherein the relative binding strength is selected so that repression dominates activation.

Bujard et al., Wasiewicz et al., Kirch et al., and Orkin make obvious a method of regulation transcription using interactions and logical operations, as discussed above. Specifically, Kirch et al. in Figure 2 teaches a scheme where transcription is not repressed in only the wild type (the first out of five configurations or clauses); consequently, repression dominates in this respect.

However, Bujard et al., Wasiewicz et al., Kirch et al., and Orkin do not teach a logic function in minimal conjunctive normal form.

The invention of Ogawa describes ranking the results of a document retrieval system. In achieving this result, Ogawa simplifies queries to conjunctive normal form as illustrated in the equations of columns 5-6 of the patent.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., and Orkin by use of the conjunctive normal form in Ogawa wherein the motivation would have been that minimal conjunctive normal form simplifies the form of the query/logical function [see equations in columns 5-6 of Ogawa]. There would have been a reasonable expectation of success in combining Bujard et al., Wasiewicz et al., Kirch et al. and Ogawa because the logic of the conjunctive normal form of Ogawa is generally applicable to the logical statements governing transcription in Bujard et al. and Kirch et al.

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Ogawa. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is stated above and reiterated below:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., and Orkin by use of the conjunctive normal form in Ogawa wherein **the motivation would have been that minimal conjunctive normal form simplifies the form of the query/logical function** [see equations in columns 5-6 of Ogawa]. There would have been a reasonable expectation of success in combining Bujard et al., Wasiewicz et al., Kirch et al. and Ogawa because the logic of the conjunctive normal form of Ogawa is generally applicable to the logical statements governing transcription in Bujard et al. and Kirch et al.

35 U.S.C. 103 Rejection #6:

Claims 10 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in

view of Ogawa as applied to claims 1, 3, 5, 7-8-9, 11, 13, 15, and 17-19 and 21 above, and further in view of Gardner et al. [Nature, 2000, volume 403, pages 339-343]

Claims 10 and 20 are further limiting comprising after the step of identifying the at least one logical function:

--reducing the at least one logic function to a minimal disjunctive normal form; and

--implementing a first clause as a repression clause and all remaining clauses as activation clauses.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin and Ogawa make obvious a method of regulation transcription using logical interactions and logical operations, as discussed above. Specifically, Ogawa teaches a disjunctive normal form in Example 1 on columns 7-8 in order to simplify document queries.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, and Ogawa, however, do not teach as a single repression clause with the remaining clauses being activation clauses.

The article of Gardner et al. studies construction of a genetic toggle switch in E. coli.

Specifically, Gardner et al. engineers a switch such as in Figure 3 on page 340 using the principles of Figure 1 on page 339 for the purpose of producing a gene-regulatory circuit. In Figure 3 of Gardner et al., there is a single repressor block and multiple activation (i.e. promoter) blocks.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al.,

Wasiewicz et al., Kirch et al., Orkin et al., and the disjunctive normal form of Ogawa by use of the activation schemes of Gardner et al., because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the combination of the Bujard et al., Wasiewicz et al., Kirch et al., Ogawa and Gardner et al. yields a switch wherein activation dominates. There would have been a reasonable expectation of success in combining these four studies because the switch of Gardner et al. is an alternate means of regulating gene expression to which the methods of Bujard et al., Kirch et al., and Ogawa are applicable.

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Gardner et al. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can be established by showing a rationale commensurate with the decision of *KSR v. Teleflex*, 550 U.S. 398 (2007). The specific rationale for this combination of references is reiterated below:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin et al., and the disjunctive normal form of Ogawa by use of the activation schemes of Gardner et al., because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the combination of the Bujard et al., Wasiewicz et al., Kirch et

al., Ogawa and Gardner et al. yields a switch wherein activation dominates. There would have been a reasonable expectation of success in combining these four studies because the switch of Gardner et al. is an alternate means of regulating gene expression to which the methods of Bujard et al., Kirch et al., and Ogawa are applicable.

35 U.S.C. 103 Rejection #7:

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21 above, and further in view of Kirchhamer et al.

Claim 22 is further limiting wherein the control functions are modular.

Bujard et al. and Wasiewicz et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al. and Wasiewicz et al. do not show that each of their processes is modular (i.e. portable or movable).

Kirchhamer et al. studies modular cis-regulatory organization of developmentally expressed genes with specific examples including two genes transcribed in the sea urchin embryo (see page 9323, column 2, of Kirchhamer et al. for an example of modular functions).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcriptional regulation and computational methods of Bujard et al. and Wasiewicz et al., by use of the modular cis-regulatory functions of Kirchhamer et al. wherein the motivation would have been that by understanding the subelements of the cis-regulatory systems as control modules, a more overall pattern of developmental gene expression can be assembled and understood [see last sentence of the introduction on page 9322 of Kirchhamer et al.]

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Kirchhamer et al. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

35 U.S.C. 103 Rejection #8:

Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21 above, and further in view of Orkin.

Claim 23 is further limiting wherein the relative binding strengths and relative binding sites within the cis-regulatory region are selected to produce specific DNA protein interactions and non-specific glue-like protein-protein interactions. (For the purposes of examination, "non-specific glue-like" protein-protein interactions are interpreted to be protein-protein interactions.)

Claim 24 is further limiting comprising selecting the relative binding strengths and relative binding sites to permit distal activation and repression.

Bujard et al. and Wasiewicz et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

However, Bujard et al. and Wasiewicz et al. does not show protein-protein interactions.

The review of Orkin studies the regulations of genes in globins. Specifically, the summary of the Orkin states on page 671:

> We can be optimistic that further dissection of LCRs will delineate DNA sequences critical for these effects and associated proteins. The interaction of LCRs with individual genes mist depend on specific protein-protein interactions , most likely involving a small, but elite, group of regulators.

Consequently, specific protein-protein interactions affect the transcription of erythroid related genes at "locus controlled regions."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify method of gene regulation of Bujard et al. by use of the protein-protein interactions in Orkin wherein the motivation would have been that comprehending specific protein-protein interactions has a significant role in understanding developmentally regulated, multigene loci not specific to globins [see summary of Orkin on page 671].

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Orkin. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations and therefore the instant modified prior art rejection is maintained.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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(EBC) at 866-217-9197 (toll-free).

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Russell S. Negin
9 January 2009

/Marjorie Moran/
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